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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,787	01/10/2002	Chong-Sheng Yuan	466992000221	9117

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/043,787	YUAN, CHONG-SHENG	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 December 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *7*.

   Claim(s) rejected: *1,3,4,6 and 8-35*.

   Claim(s) withdrawn from consideration: *36-50*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

ADVISORY ACTION

1. Claims 1, 3-4, 6-50 are pending.

2. The request for entering amendments to claims 1, 18, cancellation of claim 2, and arguments filed on 12/15/2004 under 37 CFR 1.116 in reply to the Final Action mailed on 9/9/2004 are acknowledged. The proposed amendments to the claims will be entered. While amendments to the claims seem to overcome the objections and the 35 USC 112, second paragraph rejections, they are not deemed sufficient to overcome the 35 USC 112, first paragraph and double patenting rejections previously applied for the reasons of record and those set forth below.

3. Claims 1, 3-4, 6, 8-35 would remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

4. Applicants argue that the specification provides functional characteristics coupled with a known correlation between structure and function. Applicants refer to the teachings of Creedon et al. (J. Biol. Chem. 269:16364-16370, 1994; cited in the IDS) in support of the argument that SAH hydrolases known in the art are highly conserved and that residues proposed to have roles in catalysis or substrate/coenzyme binding are identical for rat and human. Therefore, it is Applicant's contention that with what is known in the art, one of skill in the art can mutate residues directly or indirectly involved in catalytic activity in any mammalian SAH hydrolase to obtain mutant mammalian SAH hydrolases having attenuated catalytic activity and binding affinity for Hcy, SAH or adenosine. Applicants submit that the Examiner has not provided a reasonable basis for the argument that what is known in the art in regard to human and rat SAH hydrolases could not be applied to other mammalian hydrolases. Furthermore, Applicants submit that the references cited by the Examiner do not support the argument that disclosure of a few species from human, mouse and rat is not sufficient to adequately describe the entire mammalian genus of SAH hydrolases.

5. Applicant's arguments have been fully considered but are not deemed persuasive. The Examiner acknowledges the teachings of Creedon et al. as well as the teachings of the art regarding the crystal structure of the human and rat SAH hydrolases known. However, it is reiterated herein that neither the specification nor the art provide any information as to the level of structural conservation among all mammalian SAH hydrolases and the structural elements most likely to be conserved among all mammalian SAH hydrolases, such that one of skill in the art can predict the structures of other mammalian SAH hydrolases with the only species known, i.e. one mouse, one human, and several rat SAH hydrolases. Furthermore, as previously indicated in the Final Action, there is no clue as to the structural elements in all mammalian SAH hydrolases which are most likely to be variable and the role of this variability in SAH hydrolase activity or binding affinity. Therefore, contrary to Applicant's assertion, neither the art nor the specification provide a correlation between structure and function for the entire genus of mammalian SAH hydrolases recited in the claims.

6. Claims 1, 3-4, 6, 8-35 would remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for assaying Hcy, SAH, or adenosine with a mutant SAH hydrolase, wherein said SAH hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1 and also has specific substitutions at the positions recited in claim 7 and those positions disclosed in the specification, wherein said mutant SAH hydrolase has attenuated 3'-oxidative activity, 5'-hydrolytic activity, and/or 3' reduction activity, and the same, or higher, binding affinity for Hcy, SAH or adenosine when compared to the polypeptide of SEQ ID NO: 1, wherein the mutant SAH hydrolase can be labeled and wherein a labeled Ado-Cys or Ado-5'ester can be used, does not reasonably provide enablement for (1) a method for assaying Hcy, SAH, or adenosine using any mammalian-derived mutant SAH hydrolase having the functional characteristics recited in the claims, (2) the method of (1). further comprising detecting cholesterol and/or folic acid in the sample by any means, or (3) the method of (1) further comprising detecting cholesterol and/or folic acid in a sample by any means, wherein the mutant SAH

hydrolase comprises SEQ ID NO: 1 and also has the amino acid substitutions recited in claim 7 or in the specification.

7. Applicants argue that they are not required to provide disclosure of every species in a genus. Applicants reiterate that SAH hydrolases are highly conserved and that the Examiner has not provided a reasonable basis for the argument that working examples are not representative of the genus. Furthermore, Applicants argue that the presence of inoperative embodiments does not render a claim non-enabled. Applicants argue that the Examiner's rejection is based on personal knowledge and that the Examiner has not provided evidence showing SAH hydrolases with very little structural homology to what is known in the art. With regard to claim 35, Applicants argue that the claim does not have the limitation of performing cholesterol and/or folic acid after detecting binding of Hcy, SAH or adenosine. It is Applicant's contention that a sample may be split in several portions and different methods may be used for detecting different substances.

8. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner acknowledges the teachings of the prior art and agrees that (1) not all species in a genus have to be disclosed, and (2) some inoperative embodiments do not necessarily render a claim non-enabled. However, it is noted that in the instant case the genus of mammalian SAH hydrolases required is an extremely large genus and the specification fails to provide (1) the structures of all wild-type mammalian SAH hydrolases or a correlation between structure and function among all mammalian SAH hydrolases, (2) the specific amino acid residues in all wild-type mammalian SAH hydrolases which can be modified such that the required functional characteristics recited in the claims are display, and (3) the amino acid residues which can be used to substitute those found in the wild-type mammalian SAH hydrolases to obtain the mutant SAH hydrolases. As indicated above, while some rat, mouse and human SAH hydrolases are known, and it is suggested that there is high conservation in evolution among SAH hydrolases, there is no teaching in the specification or the art regarding the level of structural conservation

found among all mammalian SAH hydrolases, i.e. % structural homology, the level of variability, and the effect of that variability in SAH hydrolase activity or binding affinity to Hcy, SAH or adenosine. Neither the art nor the specification provide a correlation between structure and function for all the species in the genus.

The Examiner acknowledges that the references provided in regard to the unpredictability of the art in regard to the assignment of function based solely on structural homology do not address specifically SAH hydrolases (enzymes). However, as previously indicated, these references do show how even small structural changes have a major impact on a variety of enzymatic functions. Neither the specification nor the art indicate (1) the level of structural conservation required to display SAH hydrolase activity in all mammalian SAH hydrolases, (2) a correlation between structure and function sufficient for one of skill in the art to accurately predict the structure of any mammalian SAH hydrolase, (3) how those structural elements which are variable in any mammalian SAH hydrolase correlate with the functional limitations required in the mutants. Therefore, one cannot reasonably conclude that the claimed invention can be practiced without undue experimentation. In regard to claim 35, while it is agreed that a sample can be split into two or more portions and different methods can be used for detecting different compounds in the portions, it is noted that the claim recites "the method of claim 1 further comprising detecting cholesterol and/or folic acid in the sample". Thus, it is clear that at least one embodiment of the claim is a method where cholesterol and/or folic acid is detected after assaying Hcy, SAH or adenosine in the sample since claim 35 is further limiting the method of assaying Hcy, SAH or adenosine of claim 1.

9. Claims 1, 3, 6, 8-9, 18-19, 23-24, 30-34 would remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-14, and 16 of U.S. Patent No. 6376210. Applicants submit that they will address the double patenting rejection when allowable subject matter is identified. In view of the fact that no arguments have been presented which point out disagreements with the Examiner's position, no amendments to the claims have been made

which change the scope of the claims such that they would overcome the rejection, and no terminal disclaimer has been filed, the instant rejection is maintained for the reasons of record.

10. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: 7

Claim(s) rejected: 1, 3-4, 6, 8-35

Claim(s) withdrawn from consideration: 36-50

11. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
January 14, 2005